

ditional blood pressure control. She was also taking triazolam 0.25 mg at night and dothiepin hydrochloride 25 mg at night, both of which she had taken for many years.

Seven days after starting taking indapamide she developed a generalised, erythematous pruritic rash, confusion, and fever and was admitted to hospital. Over the next three days widespread peeling of the epidermis developed and Nikolsky's sign was present. The areas worst affected were the upper trunk, limbs, and buttocks. Among the mucosal surfaces only the buccal mucosa was affected.

She concurrently had fever with a temperature of 40.5°C, confusion, hypotension (systolic blood pressure 60 mm Hg), acute renal failure (urea concentration 46 mmol/l), and disseminated intravascular coagulation (concentration of fibrin degradation products 64 mg/l, platelet count  $51 \times 10^9/l$ ). Supportive treatment was started with intravenous fluids, fresh frozen plasma, and intravenous hydrocortisone 200 mg four times a day for 10 days, after which time the treatment was reduced. She was nursed on a ripple bed and silver sulphadiazine was applied daily to the areas of skin loss.

After five days her condition began to improve, and after a further two weeks her renal function and coagulation had returned to normal and epidermal regeneration was complete.

Indapamide is a non-thiazide diuretic used to treat essential hypertension. It is prepared by condensing a chlorosulphonamide acid chloride with an indole amine. Rashes associated with indapamide have been reported and, though usually mild, can be severe.<sup>14</sup>

Though toxic epidermal necrolysis is a well known side effect of sulphonamide drugs,<sup>5</sup> it has not previously been associated with indapamide to our knowledge. As indapamide is a commonly used drug we believe that the possibility of this side effect should be borne in mind.

We thank Mrs G Cully for typing and Dr T A J Dawson for his advice.

- 1 Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. *Br J Dermatol* 1956;68:355-61.
- 2 Pye RJ. Toxic epidermal necrolysis. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH, Burton JL, eds. *Textbook of dermatology*. Vol 2. 4th ed. Oxford: Blackwell Scientific, 1986:1658-9.
- 3 Association of the British Pharmaceutical Industry. *ABPI data sheet compendium 1990-91*. London: Data Pharm Publications, 1990:1602.
- 4 Stricker BHCh, Biriell C. Skin reactions and fever with indapamide. *BMJ* 1987;295:1313-4.
- 5 Guillaume JC, Roujeau JC, Penso D, Reuz J, Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol* 1987;123:1166-70.

## Cholestasis associated with cinnarizine

Drs STEVEN F MOSS and JULIAN R F WALKER and Ms KATE A TONGE (Royal Postgraduate Medical School, London W12 0NN) write: A 70 year old man was admitted to hospital with a three week history of progressive jaundice associated with pruritus, anorexia, loss of 12 kg, dark urine, and pale stools. He had no risk factors for infectious hepatitis and no relevant history. He had been taking triazolam for insomnia for seven months, and cinnarizine 15 mg three times a day had been prescribed for dizzy spells three weeks before jaundice developed. He had no known drug allergy and was teetotal.

On examination he was deeply jaundiced and had no fever. His abdomen was soft with no palpable masses or organomegaly and a rectal examination showed clay coloured faeces. Investigations showed an elevated bilirubin concentration of 117  $\mu\text{mol/l}$ , alkaline phosphatase activity 281 IU/l (normal range 30-130 IU/l), aspartate aminotransferase activity 71 IU/l, and  $\gamma$ -glutamyl-transferase activity 291 IU/l. He had normal renal function and electrolyte concentration. His white

cell count was  $3.8 \times 10^9/l$  with a normal differential, erythrocyte sedimentation rate was 46 mm in the first hour, and concentration of C reactive protein 9 mg/l. Coagulation studies gave normal results. Screens for haemolysis gave negative results and antibodies to hepatitis A and B viruses were not detected. An autoantibody screen showed a low titre of antibodies to smooth muscle cells ( $<1$  in 40). The biliary tree and intrahepatic ducts were not dilated, and the liver parenchyma seemed normal on ultrasonography and computed tomography. Percutaneous liver biopsy showed appreciable canalicular cholestasis, consistent with a drug reaction.

Both thiazolam and cinnarizine were stopped when he was admitted to hospital, and a month after presentation his symptoms and results of tests of liver function began slowly to improve. Liver function returned to normal after three months, when he was asymptomatic.

His cholestasis seems to have been caused by an idiopathic drug reaction. Other causes have been reasonably excluded. Many drugs may cause jaundice by various mechanisms, usually in the first three months of treatment.<sup>1</sup> Triazolam has been suggested to have caused a fatal intrahepatic cholestasis in one patient,<sup>2</sup> but the time of onset strongly implicates cinnarizine as the cause in our patient.

Cinnarizine is a piperazine derivative and is a histamine  $H_1$  receptor antagonist. It is widely prescribed for labyrinthine disorders, particularly in general practice. Approximately 40 000 prescriptions are issued each year in the United Kingdom (Department of Health; personal communication) and about 10 times this amount are purchased over the counter annually to counteract travel sickness. It is generally well tolerated with few side effects. Cinnarizine has been associated with cholestatic jaundice in two other patients, one of whom died, and with abnormal liver function in three patients, though there is no published information.

We did not rechallenge our patient with cinnarizine because of the serious liver impairment caused. We suggest that this drug caused our patient's jaundice and this cause should be considered in other similar cases.

- 1 Sherlock S. *Diseases of the liver and biliary system*. 8th ed. Oxford: Blackwell, 1989.
- 2 Cobden I, Record CO, White RWB. Fatal intrahepatic cholestasis associated with triazolam. *Postgrad Med J* 1981;57:730-1.

## Rash with intravenous fusidic acid

Mr P S STONELAKE (Birmingham General Hospital, Birmingham B4 6NF) writes: A man aged 52 had a routine total hip replacement in September 1989. Two months later there was evidence that the prosthetic joint was infected (continued hip pain, and bone lysis on radiography), and he eventually had the prosthesis removed in January 1990, when culture of tissue and fluid obtained at the operation showed both coagulase negative and coagulase positive staphylococcus. He was started on intravenous flucloxacillin (500 mg four times daily) and fusidic acid (500 mg four hours daily), with the intention of inserting a new prosthetic joint after about six weeks.

After four weeks' treatment he developed a widespread macular rash, which worsened over the next 24 hours, becoming papular. Flucloxacillin was stopped, as this was thought to be the most likely cause. The rash continued to worsen, however, over the next 24 hours, apparently with each infusion of fusidic acid, and became completely confluent. Fusidic acid was then stopped, and at the same time flucloxacillin was restarted. He improved considerably and the rash was virtually completely resolved 48 hours later. He had no associated disturbances of liver or renal

function and no haematological changes. There was no evidence that the rash was secondary to an intercurrent illness.

He did not start taking any other drug during this period apart from chlorpheniramine maleate (4 mg three times daily orally), which was given to treat the itching caused by the rash. Other drugs that he had been taking for a long time and continued to take were diazepam 10 mg at night, diclofenac 50 mg three times daily, and lofepramine 70 mg three times daily. These drugs were continued unchanged after fusidic acid was stopped. He had no history of drug allergy but had not previously taken fusidic acid.

Rashes associated with fusidic acid are rare.<sup>1</sup> The drug company concerned had had only one report of a mild transient rash to intravenous fusidic acid soon after the first administration, but other drugs were given concurrently, making it impossible to single out fusidic acid as the cause. The *Data Sheet Compendium 1990-1* does not mention rashes with fusidic acid. The Committee on Safety of Medicines had received only 12 reports of skin eruptions for all preparations containing fusidic acid up to September 1990. This case is therefore unusual, particularly in view of the late reaction after four weeks' treatment, but seems to be a genuine reaction to intravenous fusidic acid.

- 1 Dukes MNG, ed. *Meyler's side effects of drugs*. 11th ed. Amsterdam: Elsevier, 1988.

## Vasculitis related to hepatitis B vaccine

Drs P COCKWELL, M B ALLEN, and R PAGE (St James's University Hospital, Leeds LS9 7TF) write: In April 1989 a previously healthy 45 year old woman taking no concurrent medication received her first dose (20  $\mu\text{g}$  in 1 ml) of hepatitis B vaccine. Two days later she developed a pruritic rash on both feet, which over several days spread to her arms, face, and trunk. She became increasingly lethargic and breathless; developed severe Raynaud's phenomenon and a symmetrical polyarthralgia affecting her hands, wrists, elbows, and feet; and was admitted to hospital.

On examination she had a widespread maculopapular rash. No arthritis was evident. Nail bed infarcts were present and auscultation of her chest showed fine inspiratory crackles at both bases. Investigations showed normal urea concentration, liver function test results, plasma viscosity, full blood count, and results of microscopic examination of the urine. Her chest radiograph showed bilateral basal alveolar infiltrates and tests of full pulmonary function showed a restrictive pattern with small lung volumes and a gas transfer corrected for lung volume of 69% of the predicted value. No viruses were detected. Autoantibodies were not detected and complement concentrations were normal. Skin biopsy showed a dermal perivascular lymphocytic infiltrate consistent with vasculitis.

She was started on prednisolone, the dose being reduced until it was stopped after two months. Her rash rapidly improved and lethargy and breathlessness resolved over several months. After a year her chest radiograph and lung volumes were normal, although her gas transfer remained mildly impaired at 73% of that predicted.

The temporal relation between vaccine administration and vasculitis proved by biopsy suggests that her problems were due to immune complex deposition. The Committee on Safety of Medicines has had no reports of hepatitis B vaccine associated with pulmonary vasculitis. Pulmonary interstitial fibrosis has been mentioned in an American report but patients had had this condition seven years previously.<sup>1</sup>

- 1 Goolsby PL. Erythema nodosum after recombinant hepatitis B vaccine. *N Engl J Med* 1989;321:1198-9.